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EDITORIAL COMMENT

Learning the Points of COMPASS-HF

Assessing Implantable Hemodynamic Monitoring in Heart Failure Patients*

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> Every [person] has to learn the points of *COMPASS* again as often as he awakes, whether from sleep or any abstraction. Not till we are lost, in other words, not till we have lost the world, do we begin to find ourselves, and realize where we are and the infinite extent of our relations.
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> —*Henry David Thoreau [emphasis added]* (1)

The litany of numbers is so frequently proclaimed that they may be losing their impact—over 5 million patients, more than 1 million hospital discharges, more than $33 billion in annual estimated cost, almost $18 million of which is related to hospitalization costs (2)—yet it remains clear that heart failure is one of the most significant and growing medical problems in the U.S. The irony is that the 175% increase in heart failure hospitalizations during the last 25 years (2) has occurred in the context of marked advancements in our understanding of the pathophysiology and treatment of heart failure, where volume overload or redistribution plays a central role in decompensation and resultant hospitalization. One would think that detecting volume overload before it resulted in decompensation sufficient to warrant hospitalization would not be a diagnostic challenge, yet the standard tools of the physical examination (3) have remained inadequate to stem this rising tide. Consequently, considerable efforts have been expended to apply more contemporary diagnostic tools to this problem.

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Multiple different approaches have been taken to reduce hospitalizations for heart failure (4). Most studies of therapeutic interventions during hospitalization for heart failure have shown no effect on rehospitalization (5–7), although ultrafiltration showed significant reductions in rehospitalization as a secondary end point (8), and the beneficial effects of discharging patients on beta-blockers has been emphasized in observational studies (9). Heart failure management programs generally seem to reduce hospitalizations (10), although the ability to extend the results to the community has been questioned. Other studies have focused on specific diagnostic tools to guide therapy. In one small study, patients randomized to B-type natriuretic peptide–guided therapy had fewer hospitalizations for heart failure (11), although other studies have not been as favorable. Telemonitoring has many advantages, allowing for frequent scheduled as well as patient-initiated evaluations (12) and flexibility to assess symptoms and a variety of signs. A recent study using telephonic monitoring of body weight showed that increases in body weight predicted heart failure hospitalizations (13); however, a previous study using the same technology was not able to show any improvement in hospitalizations of patients managed with the device, perhaps because of a 56.2% reduction in 6-month mortality in the monitored patients (14). Other methods to assess changes in body fluid have used the principle of impedance to estimate changes in fluid status in patients either through external (15) or internal (16) measurements, but their effectiveness in reducing hospitalizations has yet to be shown. In this clinical context, another technology was developed that directly measured intracardiac pressures, the implantable continuous hemodynamic monitor.

In this current issue, Bourge et al. (17) present the results of the landmark COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study, a study of 274 patients, all of whom underwent placement of an implantable continuous hemodynamic monitor (ICHM) and were subsequently randomized to an ICHM-guided management strategy (n = 134) or control group (n = 140) follow-up. The study did not meet the primary efficacy end point of reduction in the rate of heart failure–related events, but it provides encouraging signals and many lessons for future studies. The ICHM in COMPASS-HF measures absolute right ventricular pressures and applies an algorithm to estimate pulmonary artery diastolic pressures, which have been shown to correlate well with pulmonary capillary wedge pressure (18). The system consists of 3 components: 1) a programmable device similar in appearance and implantation technique to a pacemaker pulse generator; 2) a transvenous lead positioned in the right ventricular outflow tract or septum; and 3) a small external device carried by the patient, which measures barometric pressure to correct the pressure monitor values.

The patients enrolled in COMPASS-HF comprise a reasonable target population with symptomatic heart failure

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(noninotrope-dependent New York Heart Association Class III/IV) on optimal medical therapy and a recent hospitalization for heart failure. The inclusion of both systolic dysfunction and diastolic heart failure patients is of particular interest and acknowledges the importance of patients with diastolic heart failure in this population. All of the patients in the study had a device implanted and transmitted data, allowing for twice as much information about the safety of the device and the relationship between changes in hemodynamics and subsequent outcomes. The high rate of baseline beta-blocker and angiotensin-converting enzyme inhibitor use indicates that the patients were well treated, although it also unrealistically reduces the event rate of the trial compared with that expected in the community, where utilization rates of these agents are lower.

The end points of the study reflect the need to show that new devices are both safe and effective. The safety end points were met in COMPASS-HF, with a system-related complication-free rate of 91.5%, providing 95% confidence that the rate was not below 88.7%, with no occurrences of pressure sensor failure. The primary efficacy end point compared the rate of heart failure–related events (hospitalizations, emergency department visits, and urgent clinic visits requiring intravenous therapy) in the ICHM (0.67 events per 6 patient-months) with the control group (0.85 events per 6 patient-months; $p = 0.33$) with confidence intervals that included a 25% increase and 48% reduction in the rate.

When evaluating the clinical utility to the patient of such a standalone implantable monitoring device, a number of points need to be considered. First, the nonsignificant difference of 0.18 events per 6 patient-months does not represent the full impact on the patient. This ICHM system is only implanted for monitoring purposes, and thus, the 15 hospitalizations for complications related to the device (0.06 events per 6 patient-months), as well as the prolonged initial hospitalizations related to the device in 6 patients (0.02 events per 6 patient-months), also need to be incorporated into the potential risk–benefit analysis. Additionally, every patient requires 1 hospitalization for the implant procedure itself (277 events for 1,620 patient-months of randomized follow-up or 1.03 events per 6 patient-months). Patients were also required to wear an external pressure monitor and to invest considerable time and effort in the ICHM management strategy, with almost 25 calls per patient in the 6-month period, as well as 28% more frequent changes in their therapies compared with the control group. Although it was reassuring that these frequent changes in therapy did not result in increased adverse events, it is also clear from the study that they provided no definitive benefit, as defined in COMPASS-HF. Finally, in an era of burgeoning device therapy for the treatment of heart failure, there is an opportunity cost to using the limited subclavicular implantable "real estate" for a purely diagnostic device.

The COMPASS-HF study was conducted at leading heart failure centers, using sensitive and frequent measurements of intracardiac hemodynamics, with approximately weekly contact with a health care provider; how could the COMPASS-HF study have failed to meet its efficacy end point? The answer to this question provides the bearings for future studies in this field. First, one must consider the possibility that right-sided hemodynamics do not provide the requisite information for preventing heart failure hospitalizations. Perhaps the measures are not accurate enough, the physicians did not know how to interpret or apply the data, or the paradigm of hemodynamic monitoring itself is flawed. Second, prevention of heart failure events relies on the ability to provide appropriate, timely, and effective therapy. Additional information from the COMPASS-HF study on the treatment algorithms and implementation of therapies may provide important insight into the relationship between the therapeutic interventions and clinical outcomes. These first 2 possibilities seem unlikely, but third, and most likely, is that the study design itself may have contributed to the inability to show the efficacy of ICHM. The COMPASS-HF investigators were assiduous in maintaining the single-blind state of the study, such that the control group received on average almost weekly calls. Patients in COMPASS-HF had approximately 1.8 events per 6 patient-months before enrollment in the study, a rate that decreased by over 50% in the control group. What is the appropriate visit frequency in a control group in a management strategy trial? If the control group does not receive the same number of calls or visits, how will observed differences in management strategies be interpreted? A 3-arm trial consisting of the intervention arm, a control group balanced for health care interactions, and another control group with standard care may address this issue, but how will the blinding to management group assignment be maintained? Adaptive trial designs that can account for lower-than-anticipated event rates can address some of these issues.

The COMPASS-HF trial was a landmark study providing many lessons for future trials, but perhaps the most important lesson is for clinicians caring for patients with heart failure: frequent interactions between patients and health care providers, in conjunction with appropriate use of therapies that improve outcomes, seems to markedly decrease heart failure-related events.

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